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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/518,190	03/02/2000	John Edward Hesketh	0623.0820001/REF	4790

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	25

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/518,190	HESKETH ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-16 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Formal Matters

A. The Request for Consideration, filed 2/10/03, has been entered into the record.

B. Claims 9-16 and 21 are pending and are the subject of this Office Action.

C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 9-16 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a rabbit beta-globin nucleic acid molecule with its 3'-UTR completely removed and substituted with the 3'-UTR of albumin or c-myc, does not reasonably provide enablement for the full breadth of claim 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to Applicants claiming any and all nucleic acid molecules which are encompassed by claim 9. Applicants have stated that they have unexpectedly discovered that, if an RNA encoding an intracellular protein is engineered to encode a signal peptide sequence (so that it will be secreted), the 3'-UTR of the mRNA encoding the intracellular protein will compete with the signal sequence, said signal sequence trying to send the mRNA to the ER and the 3'-UTR trying to send the mRNA elsewhere in the cell" (page 9 of Applicants' response filed 8/23/01 – part of Amendment B).

Figures 1 and 6 show the DNA sequences of the wild-type globin, c-myc and combinations thereof. These Figures show the full-length globin and c-myc proteins with and without an albumin signal sequence and with varying 3'-UTR regions. As can be seen from Figure 1, Applicants have produced a globin nucleic acid construct which has the *entire* globin 3'-UTR region either intact, or substituted with the *entire* intact 3-'UTR from either c-myc (an intracellular protein), or albumin. Applicants have provided no guidance or working examples of any nucleic acid construct with an altered 3'-UTR other than that of a globin protein, nor have Applicants provided any guidance or working examples of any globin construct with any type of alteration in the 3'-UTR region other than a replacement of the entire 3'-UTR. Applicants have not demonstrated that any alteration other than the substitution of the *entire* 3'-UTR of globin with the *entire* 3'-UTR of another nucleic acid, namely only c-myc and albumin, will lead to the mRNA being directed to the ER. This is significant since Applicants have argued that altering the 3'-UTR has unexpected results. These unexpected results would not make it predictable to one of ordinary skill in the art that anything but the entire 3'-UTR need would need to be replaced with that of another protein in order to achieve the desired results. Therefore, the artisan would not know which portions of the 3'-UTR to alter, substitute, or delete, in order to redirect the protein to the ER. In fact, respectfully, Figure 3 of the instant specification is unclear and appears that all that is required for increased localization of mRNA to the ER is a signal sequence (see construct "SSGG") and not any alteration of the 3'-UTR. Clarification of this issue is respectfully requested. Another issue is the fact that both wild-type globin and c-myc appear to be targeted, at least in part, to the ER (Figure 3), implying that some of this protein may be secreted, which is in contrast to claim 9 which states that the protein is one which is not normally secreted. As seen in the below rejection under 35 USC 103, the prior art may be enabling for the 3'-UTR-substituted constructs taught in Figure 1 of Hesketh et al., but no others. Regardless, the breadth of the present invention is still excessive.

Therefore, in summary, the breadth of the claims is excessive regarding Applicants claiming any and all nucleic acid molecules comprising any and all alterations (additions, deletions, substitutions) of any part of its 3'-UTR other than the full replacement of this region in the rabbit beta-globin mRNA. Applicants have provided no guidance or working examples of any nucleic acid construct with an altered 3'-UTR other than that of a globin protein, nor have Applicants provided any guidance or working examples of any globin construct with any type of alteration in the 3'-UTR region other than a replacement of the entire 3'-UTR. It would also not be predictable to the artisan which portions of the 3'-UTR to alter, substitute, or delete, in order to redirect the protein to the ER. For these reasons, the Examiner holds that undue experimentation is required to practice the claimed invention.

3. Claim Rejections - 35 USC § 102

A. The rejection of claims 9-12, 14-16 and 21 under 35 USC 102 has been withdrawn in view of Applicants' arguments that Scott et al. do not teach the use of a mammalian signal peptide, nor that secretion of PI-6 can be achieved by altering the 3'-UTR.

4. Claim Rejections - 35 USC § 103

A. The rejection of claims 9-12, 14-16 and 21 under 35 USC 103 has been withdrawn in view of Applicants' arguments that Scott et al. do not teach the use of a mammalian signal peptide, nor that secretion of PI-6 can be achieved by altering the 3'-UTR.

B. Claims 9-16 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hesketh et al. (reference AS on the Form PTO-1449 filed August 29, 2000) in view of Sleep et al. (on the Form PTO-892 dated 11/8/02) and further in view of Applicants' admission on the record (page 6 of the Response dated 8/8/02) that it "is well known" that "in order to obtain secretion of an intracellular protein...a nucleic acid encoding a signal peptide [must] be attached to the mRNA encoding the intracellular protein."

The claims recite a nucleic acid molecule encoding a mammalian signal peptide from a protein normally secreted from a mammalian cell operatively linked to a nucleic acid encoding a protein that would not normally be secreted from a mammalian cell, wherein the nucleic acid is either DNA or RNA. The claims also recite the use of an albumin signal sequence, vectors, cells and methods of obtaining the protein.

Hesketh et al. teach that it is already well-known, and seen in Drosophila and Xenopus oocytes that directional information for mRNAs is already known to be present in their 3'-UTR. Furthermore, Figure 2A on page 145 (left panel) that pSV-myc (see also Figure 1) is normally targeted to cytoskeletal polysomes ("C") under wild-type conditions. However, it can be seen in the right panel of Figure 2A that, upon the alteration of the 3'-UTR of c-myc by the substitution of part of that UTR with part of the 3'-UTR of the globin gene, that a portion of myc, which is a protein not normally secreted, is now targeted to membrane-bound polysomes ("M") even in the absence of a signal sequence. Hesketh et al. also teach vectors, host cells and methods for obtaining protein (see "Cell Lines and Cell Fractionation" under Materials and Methods). Hesketh et al. also teach chimeric constructs (Figure 1). Hesketh et al. do not teach the use of a signal sequence (e.g. albumin) to increase protein secretion. Similarly, as can be seen in

the right panel of Figure 2B, swapping a part of the 3'-UTR of the globin gene with that of myc also shows some targeting of the gene to membrane bound polysomes (right panel).

Sleep et al. do teach the use of a human serum albumin signal sequence to secrete a protein (Abstract). Therefore, it would have been obvious to one of ordinary skill in the art to have added one of the numerous signal sequences, including the human serum albumin signal sequence of Sleep et al. to the gene of Hesketh et al. in view of the suggestion by Sleep et al. that it would be desirable to do so, as well as in view of Applicants' admission on the record that signal sequences are well-known in the art to be required for secretion of intracellular proteins. Sleep et al. teach that in designing secretion systems for heterologous proteins, one aims to maximize both the yield and fidelity of the product and that the choice of leader sequence and its relationship to the structural protein under study are crucial to the success of the protein. One of ordinary skill in the art would have had a reasonable expectation of success in adding a nucleic acid sequence encoding a human serum albumin signal sequence as taught by Sleep et al. to the gene of Hesketh et al. since molecular cloning techniques were well-known and highly successful at the time of the present invention, as evidenced by their successful use by Sleep et al. and Hesketh et al.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 10, 2003

ROBERT LANDSMAN
PATENT EXAMINER